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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Alireza Rezaie and Charles T. Esmon

Serial No.: 08/259,321 Group Art Unit: 1642

Filed: June 10, 1994 Examiner: N.Johnson

For: CALCIUM BINDING RECOMBINANT ANTIBODY AGAINST PROTEIN C

Assistant Commissioner of Patents
Washington, D.C. 20231

**APPEAL BRIEF**

Sir:

This is an appeal from the final rejection of claims 1-3, 5, 7, 8, 14, 15, and 17-21 in the Office Action mailed March 31, 1999 in the above-identified patent application. A Notice of Appeal was filed on July 30, 1999. A Petition for an Extension of Time for three months, up to and including December 30, 1999, and the appropriate fee for the extension and for the filing of this Appellants' Brief are enclosed. Also enclosed is an Amendment in response to the objection to the Sequence listing.

## (1) REAL PARTY IN INTEREST

The real party in interest of this application is the Oklahoma Medical Research Foundation, Oklahoma City, OK.

## (2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

## (3) STATUS OF CLAIMS ON APPEAL

Claims 1-3, 5, 7-8, 14, 15, and 17-21 are pending and on appeal.

## (4) STATUS OF AMENDMENTS

The claims were last amended by the Amendment mailed December 31, 1998. An Amendment to correct a typographical error in claim 2 and the reference to sequence listing in claims 2 and 15 accompanies this Appeal Brief. The text of each claim on appeal, prior to entry of this amendment, is set forth in the Appendix to this Appeal Brief. An Appendix including the claims as amended by the Accompanying Amendment is attached to the Amendment.

## (5) SUMMARY OF THE INVENTION

The claimed invention is a recombinant antibody having a unique specificity for a peptide region of Protein C (a blood clotting factor) in combination with calcium ions (page 7 and page 9, lines 2-3), and method of making. The recombinant antibody is made by recombination and expression of the cloned nucleotide sequences encoding the variable regions of a unique murine

antibody. The murine antibody is described in U.S. patent Nos. 5,147,638 and 5,202,253 to Esmon, et al. (page 4, lines 8-18). The recombinant antibody is defined in claim 1 of this application as either humanized or expressed in bacterial or insect cells, to differentiate the murine antibody disclosed in the '638 Esmon patent. As described in the '638 Esmon patent, the murine antibody was used to demonstrate that an antibody promoting blood coagulation by interfering with native protein C was effective in treating tumors (page 4, lines 8-18). However, clinical trials in humans could not be initiated using a murine antibody, since repeated injections were required, and a humanized antibody was needed (page 5, lines 25-28). It was not possible to create a humanized antibody without first cloning the nucleotide sequence encoding the variable regions of the HPC-4 antibody described in the '638 Esmon patent. Since the binding specificity of this antibody is so unusual, even upon cloning it was difficult to predict whether the humanized antibody would have the same binding specificity for both calcium ions and the peptide epitope of the protein C. The intimate role of the calcium ions has been demonstrated by showing that the antibody binds protein C only in th presence of calcium, but that the protein and antibody can be separated simply by removing the calcium using EDTA, a calcium chelator.

## (6) ISSUES ON APPEAL

The issues presented on appeal are

(1) whether claims 1, 2, 3, 5, 7, 8, 14, 15, and 17-21 should be rejected under 35 U.S.C. §103 as obvious over U.S. Patent No. 5,202,253 or 5,147,638 to Esmon, et al, D'Angelo, et al., J. Clin.

Invest. 77, 416-425 (1986) or Stearns, et al., J. Biol. Chem. 263(2) 826-832 (1988) in view of Morrison, Science 229, 1201-1207 (1985) or WO90/07861 by Protein Design Labs, Inc. ("Queen"); and

(2) whether claims 1, 2, 5, 6, 8, 14, 15 and 20 should be rejected under the doctrine of obviousness-type double patenting over U.S. Patent No. 5,202,253 to Esmon, et al. in view of Morrison, Science 229, 1201-1207 (1985) or WO90/07861 by Protein Design Labs, Inc. ("Queen").

## (7) GROUPING OF CLAIMS

Claims 1-3, 5, 7, 8, 14, 15, and 17-21 are generally drawn to a recombinant antibody binding to calcium ions in combination with a specific amino acid region of protein C, either including human constant regions or expressed in a bacterial or insect expression system, and method of making the antibody by expressing a recombinant nucleotide molecule in a bacterial or insect expression system. The claims can be distinguished by limitations to specific amino acid sequence (claims 1 (the amino acid sequence inherent in the deposited antibody, 2 (the recited amino acid sequence), 15), humanized (claims 3, 17), method for expression of nucleotide sequence encoding the antibody in bacterial or insect cells (claims 14, 15, 17-19 and 21), and antibody-protein conjugate and method for making (claims 20 and 21).

These claims must be considered separately since there are different elements (i.e., the nucleotide sequence encoding the monoclonal antibody, protein sequence derived from human,

lack of glycosylation or differences in glycosylation due to expression system (i.e., bacterial and insect versus mammalian cells)).

## (8) ARGUMENTS

### (i) The Claimed Invention

The invention was the cloning of the gene encoding the variable regions of a unique monoclonal murine antibody which is the subject of U.S. patent No. 5,202,253 to Esmon, et al. As demonstrated by the declarations under 37 C.F.R. §1.132 which were submitted during the prosecution of the '253 patent (copies of which are attached to this appeal brief for the convenience of the Board - although submitted twice during prosecution, it appears they have been misplaced from the PTO's file), this antibody, referred to as HPC-4, has a unique specificity for the combination of calcium ions and an amino acid region of the protein C coagulation factor. No other antibody has been isolatable having this unique specificity. Therefore, when it was discovered that the antibody was particularly useful in methods such as the method for killing tumors described in U.S. patent No. 5,147,638, it became particularly desirable to humanize the antibody. This required two things: (1) a nucleotide sequence encoding the variable regions of the antibody which imparted the unique specificity and (2) a showing that the protein encoded by the cloned nucleotide sequence that imparted the specificity. It was not known with certainty prior to cloning and expression of the nucleotide sequence that the encoded protein would retain the same specificity.

The recombinant antibody was also useful for other purposes, particularly in separations technology, where it is useful in separation of protein C or other proteins incorporating the protein C epitope. Large scale production of the recombinant antibody in bacterial or insect cell expression systems was not possible absent cloning of the gene encoding the antibody variable regions.

**(ii) Rejections Under 35 U.S.C. § 103**

The claims to the recombinant antibody were rejected over the applicants' earlier publications and patents in view of general disclosures relating to humanization of antibodies. This rejection must fail since (1) the claimed recombinant antibodies cannot be obtained absent cloning of the gene encoding the variable regions of the antibody and it is well established under U.S. law that it is not obvious to obtain a specific nucleotide sequence based on the protein and (2) even if cloning were obvious, one skilled in the art could not have predicted that it was merely the amino acid sequence forming the variable regions of the HPC-4 murine antibody that was responsible for the unique protein-calcium binding specificity of the antibody.

**a. The Legal standard for Obviousness.**

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention

would have a reasonable likelihood of success. *In re Dow Chemical Company,* 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989).

As discussed in more detail below, the prior art did not suggest cloning of the murine HPC-4 antibody but instead argued that it was a unique antibody with a unique binding specificity that could not be obtained by others using conventional means. Not only does the art not suggest cloning, but those skilled in the art (as evidenced by the accompanying Declarations) had no expectation of success in finding other antibodies with the same unusual specificity. Although the claimed recombinant antibody contains portions of the murine HPC-4 antibody, it is different from and not predictable from, the murine antibody.

Moreover, it is unarguable that the claimed recombinant antibody requires cloning of a nucleotide molecule encoding this unique murine antibody. The only art cited by the examiner with regard to cloning and expression of recombinant antibodies is general in nature. In this

respect, the current rejections are analogous to the rejection deemed improper by the Federal Circuit (*In re Deuel*, 34 USPQ2d 1210 (Fed. Cir. 1995)). In *Deuel*, the court reaffirmed that a rejection based on an "obvious to try" standard was improper. The court specifically found that prior art that teaches a method for obtaining a general result, when the actual results are unknown, is insufficient to make obvious the actual results obtained upon which the claims are based. In pertinent part, the *Deuel* court states

> "A general motivation to search for some gene that exists does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of that search."

> "Thus, even if, as the examiner stated, the existence of general cloning techniques, coupled with knowledge of a protein's structure, might have provided motivation to prepare a cDNA or made it obvious to prepare a cDNA, that does not necessarily make obvious a particular claimed cDNA. 'Obvious to try' has long been held not to constitute obviousness". Id.

Applicants point out that in *Deuel* the Patent Office made the same arguments being made in the present rejection: that it would have been obvious to isolate a claimed DNA

molecule in view of a workable method to do so taught in the prior art. Whatever the alleged scientific merits of this argument, the Federal Circuit explicitly and forcefully rejected it on legal grounds. The court in *Deuel* stated:

> [W]hile the general idea of the claimed molecules, their function, and their general chemical nature may have been obvious from [prior art] teachings, and the knowledge that some gene existed may have been clear, the precise cDNA molecules of [the claims] would not have been obvious over the [prior art] because [the prior art does not teach] . . . the claimed or closely related cDNA molecules. * * * [O]ne could not have conceived the subject matter of [the claims] based on the teachings in the cited prior art because, until the claimed molecules were actually isolated and purified, it would have been highly unlikely for one of skill in the art to contemplate what was ultimately obtained. What cannot be contemplated or conceived cannot be obvious.

The PTO's theory that one might have been motivated to try to do what Deuel in fact accomplished amounts to speculation and an impermissible hindsight reconstruction of the claimed invention. It also ignores the fact that [the claims] are limited to specific compounds, and any motivation that existed was a general one, to try and obtain a gene that was yet undefined and may have constituted many forms.

*Deuel* at 1558.

The situation here is exactly analogous. Knowledge that a gene exists is not enough. *Deuel* at 1558. The nucleic acid must be conceived before it can be obvious.[1] *Id.* It is important to note that in *Deuel* the Federal Circuit was not impressed with that fact that the corresponding gene was known to exist and the method proposed in the rejection would actually result in isolation of the claimed cDNA (Deuel had used essentially the method suggested in the rejection). Thus, the alleged workability of the method of isolating cDNA encoding the gene is irrelevant to an obviousness analysis.[2]

**b. The Prior Art Cited by the Examiner.**

Claims 1, 2, 3, 5, 7, 8, 14, 15, and 17-21 were rejected under 35 U.S.C. §103 as obvious over U.S. Patent No. 5,202,253 or 5,147,638 to Esmon, et al, D'Angelo, et al., J. Clin. Invest. 77, 416-425 (1986) or Stearns, et al., J. Biol. Chem. 263(2) 826-832 (1988) in view of Morrison, Science 229, 1201-1207 (1985) or WO90/07861 by Protein Design Labs, Inc. ("Queen").

**1. Prior Art Describing the Murine Monoclonal HPC-4 Antibody.**

**U.S. Patent Nos. 5,202,253 and 5,147,638 to Esmon**

Neither U.S. Patent No. 5,202,253 nor 5,147,638 disclose nor claim a recombinant antibody. The only specific antibody, the HPC-4 antibody, is a murine monoclonal antibody.

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[1] Relevant to this, the Federal Circuit subsequently held that a method of isolating a gene cannot provide a description of the gene. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997)

[2] See *Deuel* at 1559 ("[T]he existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves

The '253 patent is directed to the discovery and characterization of this unique murine monoclonal antibody. The '638 patent describes methods of using antibodies to protein C, such as the HPC-4 antibody, to kill tumors by inducing extensive coagulation of the tumor microvasculature. Neither patent describes, nor more importantly, enables, nor even motivates one to obtain, a recombinant antibody, and certainly provides no guidance for how the antibody could be humanized. As demonstrated by the enclosed copies of the seven Declarations under 37 C.F.R. §1.132 filed during the prosecution of these applications, the claimed murine antibody was totally unique and that was why it was patentable. It was impossible to predict that one could obtain another antibody with the same kind of reactivity.

**Stearns**

Stearns was cited as prior art to, and overcome during the prosecution of, the claimed murine monoclonal antibodies in the '638 and '253 patents. Stearns reported on the properties of the murine monoclonal HPC-4 antibody. During prosecution of the '253 application the examiner determined, based on the evidence submitted in this application, that absent the antibody, i.e., the availability of the antibody itself, not just its description, one could not make and use the HPC-4 antibody due to the unique characteristics of the antibody. If the article could not enable and make obvious the murine monoclonal antibody that it described, it certainly could not enable and make obvious cloning and expression of a recombinant antibody sharing only the variable portion of the antibody conferring the unique specificity as claimed. No amino acid or

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would have been obvious....")

nucleotide sequence is provided, nor would it be obvious from the protein.

**D'Angelo**

D'Angelo is an even less illuminating description of the murine monoclonal antibody referred to as HPC4, than the Stearns paper. Again, there is nothing that would enable the HPC4 antibody, much less cloning and manipulation so that the nucleotide molecule encoding the variable regions of the murine monoclonal HPC-4 antibody could be expressed in either bacterial cells or modified to incorporate human amino acid sequences.

It is significant that not only is there no guidance in any of this art to make a recombinant antibody having the same specificity, there is not teaching that would lead one skilled in the art to have any reasonable expectation of success, even if the gene could be cloned, until it was demonstrated that the amino acid sequence comprising the variable region of the murine HPC-4 antibody was *solely* responsible for the unique binding activity of the antibody.

**2. Prior Art Disclosing General Methods for Humanizing Antibodies.**

**Morrison and Queen**

Morrison or Queen do not make up for these deficiencies. Morrison demonstrates that genes encoding immunoglobulins (antibodies) can be transfected into cells and expressed. It is significant that at page 1206-1207 notes the difficulties in obtaining expression of functional molecules in non-lymphoid expression systems. Even as to expression in the lymphoid cells, the binding activity was shown in at least some cases to be significantly decreased (see, for example, page 1206, first column). Queen describes methods for making recombinant antibodies, much of

which amounts to constructive reduction to practice, and actually demonstrates efficacy only with a single antibody having a simple, standard affinity for a protein, IL-2 receptor.

Neither provides the enablement to clone the gene encoding the murine monoclonal HPC-4 antibody, nor provides any basis for believing that such a unique antibody could be cloned and still behave in its unique calcium dependent manner. It is clear that under §103 the art must not only motivate one to modify that which is disclosed in the prior art as applicants have done, but that there must be a reasonable expectation of success in doing so. The Examiner can point to no such support, and it is in fact contradicted by the numerous declarations filed during the prosecution of the parent applications, even more strongly supporting the patentability of the claimed humanized or recombinant antibodies.

**3. Summary**

An antibody secreted by a murine hybridoma from murine antibody genes is not the same as the claimed recombinant antibody, which is either expressed in bacterial or insect cells or has been humanized. As evidenced by the prosecution history in the '253 case, numerous experts submitted declarations under oath that even with undue experimentation they were unable to make by standard techniques monoclonal antibodies having the unique specificity of HPC-4: binding with one part of the antibody a peptide epitope and binding with another part of the antibody calcium. Until one had actually cloned the nucleotide sequence encoding HPC-4 and expressed it, it was not possible to predict that the isolated nucleotide sequence encoded HPC-4, much less whether it would be expressed in functional form and bind to both peptide and calcium

ions. As demonstrated by the examples in the application, applicants expressed recombinant fragments encoding the variable regions of the murine HPC-4 antibody and showed they have the requisite binding activity. Humanized antibodies having the same specificity were also made using standard techniques, based on the disclosed nucleotide sequence, by Genentech for use in animal trials for treatment of tumors. In the absence of the nucleotide sequence, one cannot modify and genetically engineer the antibody to include non-murine amino acid sequence.

The Examiner's position is that the nucleotide sequence is obvious from the prior disclosure of the protein, i.e., the HPC-4 antibody. In the absence of the nucleotide sequence, one could not make the claimed antibody. This position is simply contradictory to that of the Court of Appeals in In re Deuel, that merely having the protein, or even some amino acid sequence (which is not described in the claims of the issued patent) would not be sufficient. The examiner has cited no art that discloses or makes obvious the amino acid sequence encoded by the recited nucleic acid. The art which has been cited by the Examiner discloses general methods to make chimeric antibodies. This would not provide one skilled in the art with the methodology and a reasonable expectation of success that one could clone the hypervariable region of the HPC4 antibody, insert the cloned genes into an expression vector, and express antibody or antibody fragments having the requisite binding affinity. Even though the claimed subject matter is an antibody, the antibody **cannot be made except by expression of the nucleotide sequence**; accordingly, the antibody cannot be obvious from the naturally occuring antibody.

There are two basis on which the claimed antibodies are not obvious:

(1) the nucleotide sequence encoding the antibody was not known and the protein sequence of the antibody was not known, and

(2) the specificity of the antibody required the presence of two distinct molecules: calcium and a peptide epitope, a highly unusual situation for antibodies.

Applicants had attempted to make antibody fragments which had the requisite binding activity and found that the cleavage reactions generated many products, with loss of most activity. The definition of the hypervariable region, which was determined by cloning, was critical to construction and expression of defined portions of HPC4 and to humanization of the antibody. One skilled in the art simply could not have any basis for determining whether or not an antibody with the unique specificity of the HPC4 antibody could be cloned and this specificity expressed in a recombinant molecule. The Examiner has cited no evidence that one skilled in the art had ever attempted to clone such an antibody, much less had any success. The key to sustaining an obviousness rejection in this kind of situation is **not whether it was obvious to try**, but **whether one skilled in the art would have an expectation of success**. HPC4 was a highly unusual antibody. As demonstrated by the declarations submitted in the prosecution of the patents claiming HPC4, unlike most monoclonals, HPC4 was impossible to duplicate. Calcium dependent antibodies immunoreactive to protein C, obtained by other parties, simply did not share the unique reactivity where calcium is essential to binding - merely having calcium present to alter binding **affinity** was not enough. This unique reactivity was obtained in the

cloned, recombinant antibody - but this success, not well understood even after cloning, could not have been predicted.

**(iii) Double patenting Rejection**

Claims 1, 2, 5, 6, 8, 14, 15 and 20 were rejected under the doctrine of obviousness-type double patenting over U.S. Patent No. 5,202,253 to Esmon, et al. in view of Morrison, Science 229, 1201-1207 (1985) or WO90/07861 by Protein Design Labs, Inc. ("Queen").

**a. The Legal Standard of Obviousness Type Double Patenting.**

There are two types of double patenting rejections. One is "same invention" type double patenting, prohibited by 35 U.S.C. §101, where the claims of the application in question would be literally infringed by those in the other application or patent in question. Application of Vogel, 422 F.2d 438, 441 (C.C.P.A. 1970; M.P.E.P. §804. The other type of double patenting rejection is "obviousness-type" double patenting, in which there is no "patentable difference" between the claims of the application at issue and the claims of the other application or patent, or, stated another way, the claims in the application are an obvious variation over the claims in the other application or patent. It is a judicially-created doctrine. General Foods v. Studiengesellschaft Kohle MbH, 972 F.2d 1272, 1278-1279 (Fed. Cir. 1992; In re Braat, 937 F.2d 589, 592 (Fed. Cir. 1991); Vogel, at p. 441. An obviousness type rejection is "analogous to [a failure to meet] the non-obviousness requirement of 35 U.S.C. §103, except that the patent principally underlying the double patenting rejection is not considered prior art." In re Longi, 759 F.2d 887, 892, n. 4. (Fed. Cir. 1985), *citing* In re Braithwaite, 379 F.2d 594, 600, n. 4 (C.C.P.A.

1967)

A proper double patenting rejection must consider the claim as a whole, including all limitations. General Foods, at p. 1278; Carman v. Wahl, 724 F.2d 932, 940 (Fed. Cir. 1983); *cf.* Ex Parte Crissy, 201 U.S.P.Q. (BNA) 689, 693 (P.O.B.A. 1976). The disclosure of an issued patent cannot be used as prior art, even when the disclosure is in the claims. General Foods, at p. 1281.

**b. The claimed recombinant antibody is not obvious from the claimed murine monoclonal HPC-4 antibody.**

Therefore, the same general analysis as under §103 is applied under the doctrine of obviousness-type double patenting, but with regard solely to the issue of whether the claims in this application are obvious over the claims in the issued patent. For the same reasons that the claims are not obvious in view of the disclosures of these patents, they are even less obvious from the claims. The claimed murine antibody, and methods of use thereof, do not make obvious the nucleotide sequence required to make the recombinant antibody, nor is it predictable that even if one did clone the antibody, that the unique binding characteristics of HPC-4 would be transferred to the recombinant antibody.

As discussed above, Esmon discloses a unique monoclonal murine antibody reactive with two elements: calcium and a peptide present in protein C. It was not obvious from Esmon alone or in combination with the references detailing preparation of monoclonal antibodies and humanized antibodies that one could humanize this unique monoclonal antibody and still retain

the unique reactivity.

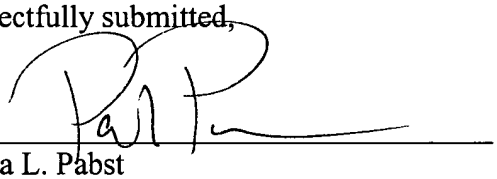
## (9) SUMMARY

There is no description in the prior art of a nucleotide sequence encoding the variable regions of the murine HPC-4 monoclonal antibody, nor a motivation and teaching that would lead one of ordinary skill in the art to clone the murine HPC-4 murine HPC-4 monoclonal with a reasonable expectation of success to make a recombinant antibody.

## (10) CONCLUSION

Reversal of the rejections under 35 U.S.C. §103 and under the doctrine of obviousness type double patenting and allowance of all claims 1, 3-5, 7, 8, 14, 15, and 17-21 is earnestly solicited.

Respectfully submitted,



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## APPENDIX: Claims on Appeal

1. A recombinant $Ca^{2+}$ dependent monoclonal antibody or antibody fragment including a heavy chain and a light chain, wherein the antibody or antibody fragment comprise the hypervariable regions of the monoclonal antibody produced by the hybridoma deposited with the American Type Culture Collection as ATCC No. HB 9892 which bind an epitope in the activation peptide region of the heavy chain of Protein C defined by E D Q V D P R L I D G K (Sequence ID No. 1) and calcium ions, where the antibody and antibody fragment inhibit Protein C activation by thrombin-thrombomodulin, and wherein the antibody and antibody fragment are expressed in bacterial or insect cells or is humanized.

2. The antibody of claim 1 comprising an amino acid sequence selected from the group consisting of:

MGRLSSSFLL LIAPAYVLSQ VTLKESGPGI LQPSQTLTLT CSLSGFSLRT SGMGVGWIRQ PSGKGLEWLA HIWWDDDKRY NPVLKSRLII SKDTSRKQVF LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (Sequence ID No. 10); MDFQVQIFSF LLISASVIMS RGQIILTQSP AIMSASLGEE ITLTCSATSS VTYVHWYQQK SGTSPKLLIY GTSNLASGVP SRFSGSGSGT FYSLTVSSVE AEDAADYYCH QWNSYPHTFG GGTKLEIKR (Sequence ID No. 12); Q VTLKESGPGI LQPSQTLTLT CSLSGFSLRT SGMGVGWIRQ PSGKGLEWLA HIWWDDDKRY NPVLKSRLII SKDTSRKQVF LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (amino acids 20-139 of Sequence ID No. 10) and QIILTQSP AIMSASLGEE ITLTCSATSS

VTYVHWYQQK SGTSPKLLIY GTSNLASGVP SRFSGSGSGT FYSLTVSSVE

AEDAADYYCH QWNSYPHTFG GGTKLEIKR (amino acids 23-129 of Sequence ID No. 12).

3. The antibody of claim 1 which is humanized.

5. A composition comprising the antibody of claim 1 in combination with a pharmaceutically acceptable carrier for administration to a patient.

7. The antibody of claim 1 having a detectable label directly bound to the antibody.

8. The antibody of claim 1 immobilized to a substrate which does not interfer with binding of the antibody to protein C in combination with calcium ions, wherein the immobilized antibody is suitable for purification of protein C from a biological fluid.

14. A method of making a recombinant $Ca^{2+}$ dependent monoclonal antibody which binds an epitope in the activation peptide region of the heavy chain of Protein C defined by E D Q V D P R L I D G K (Sequence ID No. 1) and calcium ions, where the antibody inhibits Protein C activation by thrombin-thrombomodulin, by expressing nucleotide molecules encoding the hypervariable region of the heavy and light chains of the monoclonal antibody expressed by the hybridoma deposited with the American Type Culture Collection as ATCC No. HB 9892 in bacteria or insect cells.

15. The method of claim 14 wherein the antibody comprises an amino acid sequence selected from the group consisting of:

MGRLSSSFLL LIAPAYVLSQ VTLKESGPGI LQPSQTLTLT CSLSGFSLRT

SGMGVGWIRQ PSGKGLEWLA HIWWDDDKRY NPVLKSRLII SKDTSRKQVF

LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (Sequence ID No. 10); MDFQVQIFSF LLISASVIMS RGQIILTQSP AIMSASLGEE ITLTCSATSS VTYVHWYQQK SGTSPKLLIY GTSNLASGVP SRFSGSGSGT FYSLTVSSVE AEDAADYYCH QWNSYPHTFG GGTKLEIKR (Sequence ID No. 12); Q VTLKESGPGI LQPSQTLTLT CSLSGFSLRT SGMGVGWIRQ PSGKGLEWLA HIWWDDDKRY NPVLKSRLII SKDTSRKQVF LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (amino acids 20-139 of Sequence ID No. 10) and QIILTQSP AIMSASLGEE ITLTCSATSS VTYVHWYQQK SGTSPKLLIY GTSNLASGVP SRFSGSGSGT FYSLTVSSVE AEDAADYYCH QWNSYPHTFG GGTKLEIKR (amino acids 23-129 of Sequence ID No. 12).

17. The method of claim 14 wherein the antibody is humanized.

18. The method of claim 14 further comprising directly binding detectable label to the antibody.

19. The method of claim 14 further comprising immobilizing the antibody to a substrate which does not interfer with binding of the antibody to protein C in combination with calcium ions, wherein the immobilized antibody is suitable for purification of protein C from a biological fluid.

20. The recombinant antibody of claim 1 having coupled thereto a peptide sequence.

21. The method of claim 14 wherein the nucleotide sequence encoding the recombinant antibody is ligated to a sequence encoding a peptide and the ligated nucleotide sequence is expressed in an expression system.

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Certificate of Mailing


**Certificate of Mailing under 37 CFR § 1.8(a)**

I hereby certify that this Appeal Brief and Exhibits, Amendment, and Petition for Extension of Time, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Patrea L. Pabst

Date: December 30, 1999